BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

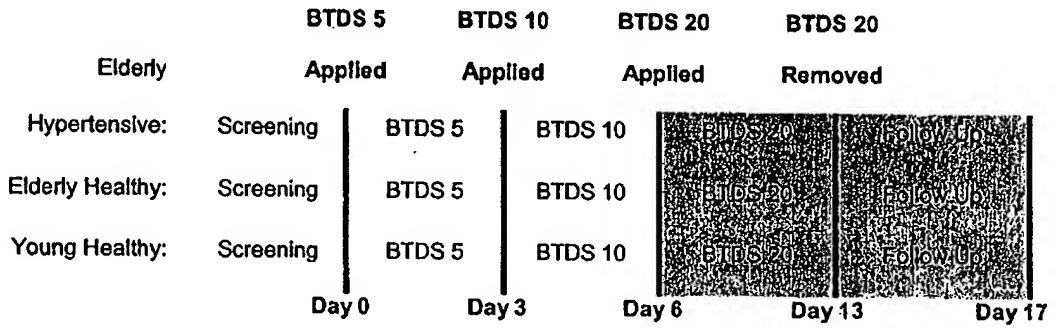
Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Problem Image Mailbox.

Vital Sign Assessments – BP, Pulse, Respiratory Rate, SaO_2			
0, 1, 4, 8, 12, 24 h preapplication of BTDS 5	Day 0 and 3 at 30 min, prior and 1, 2, 4, 8, 12, 20, 23, 36, 47, and 60 h post-application of BTDS 5 and BTDS 10	Day 6 at 30 min, prior and 1, 2, 4, 8, 12, 20, 23, 36, 47, 60, 71, 84, 95, 108, 119, 132, 143, 156, and 164 h postapplication of BTDS 20	Day 13 and at 0.25, 0.50, 0.75, 1, 2, 4, 8, 12, 24, 48, and 72 h postremoval of BTDS 20



0, 23, and 47 h postapplication of BTDS 5 and BTDS 10	0, 23, 47, 71, 95, 119, and 143 h postapplication of BTDS 20	0.25, 0.50, 0.75, 1, 2, 4, 8, 12, 24, 48, and 72 h post-removal of BTDS 20

Pharmacokinetic Sampling

FIGURE 1

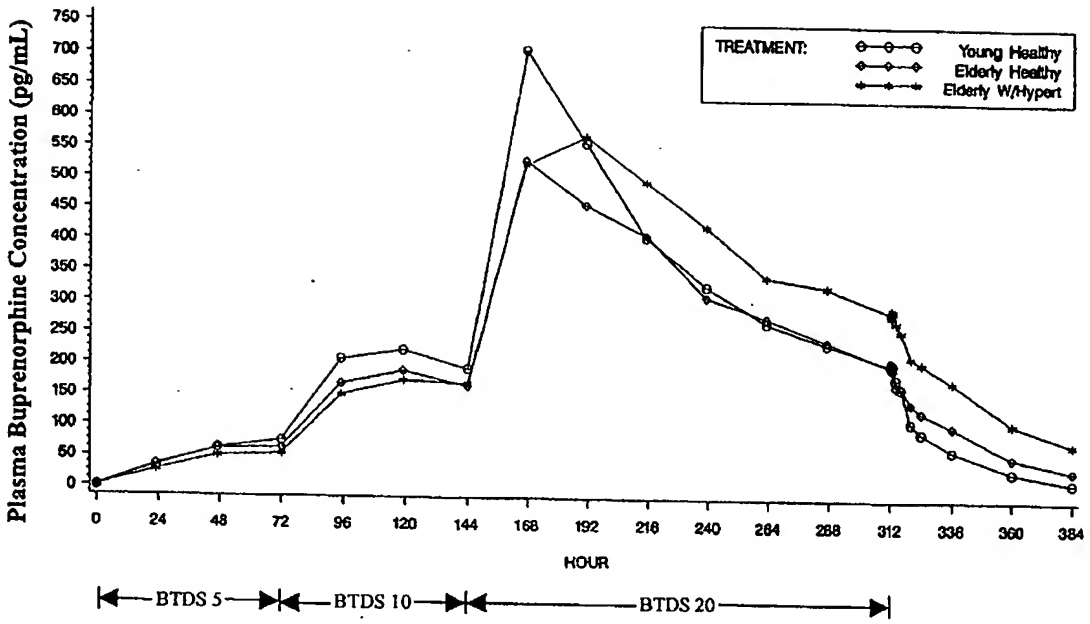

Plasma Buprenorphine Concentration (pg/mL)
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
TREATMENT:
Young Healthy
Elderly Healthy
Elderly W/Hypert
0
24
48
72
96
120
144
168
192
216
240
264
288
312
336
360
384
HOUR
BTDS 5
BTDS 10
BTDS 20

FIGURE 2

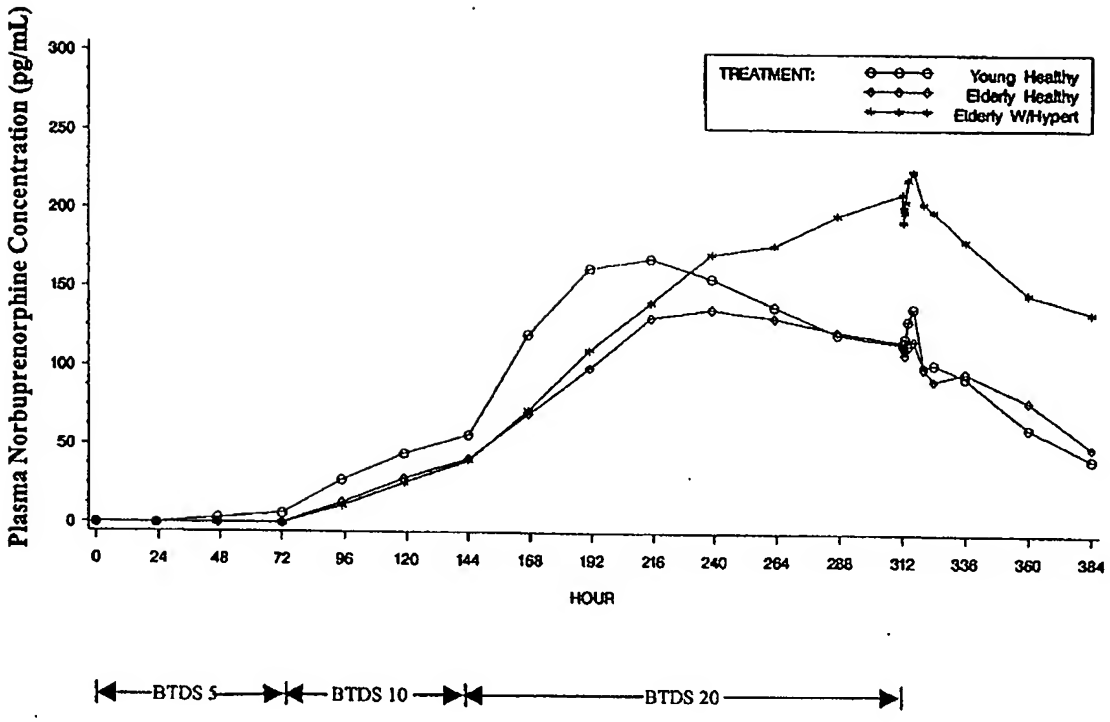
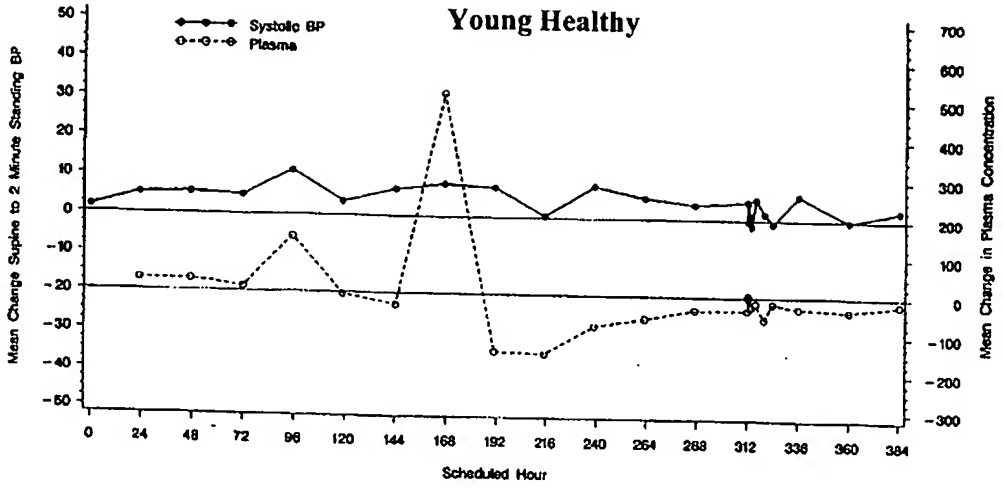
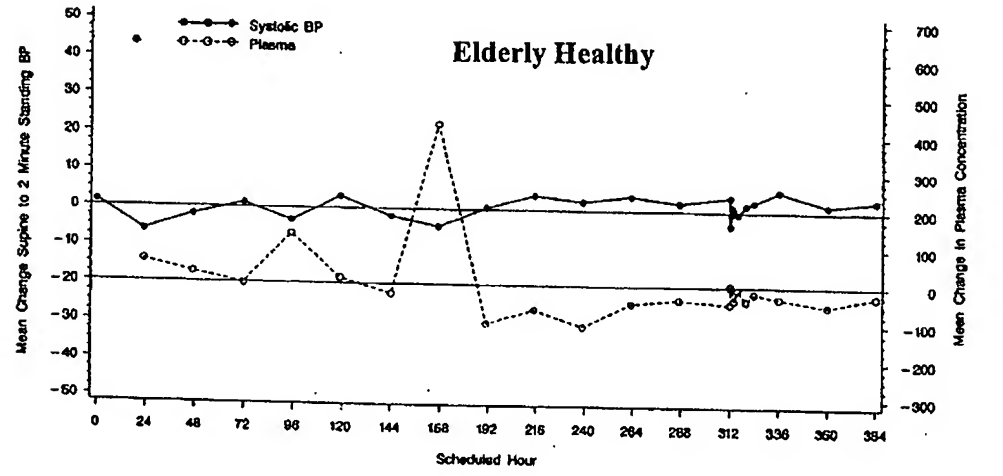

Plasma Norbuprenorphine Concentration (pg/mL)
300
250
200
150
100
50
0
TREATMENT:
Young Healthy
Elderly Healthy
Elderly W/Hypert
0
24
48
72
96
120
144
168
192
216
240
264
288
312
336
360
384
HOUR
BTDS 5
BTDS 10
BTDS 20

FIGURE 3


Young Healthy
Systolic BP
Plasma
Mean Change Supine to 2 Minute Standing BP
Mean Change in Plasma Concentration
Scheduled Hour


Elderly Healthy
Systolic BP
Plasma
Mean Change Supine to 2 Minute Standing BP
Mean Change in Plasma Concentration
Scheduled Hour

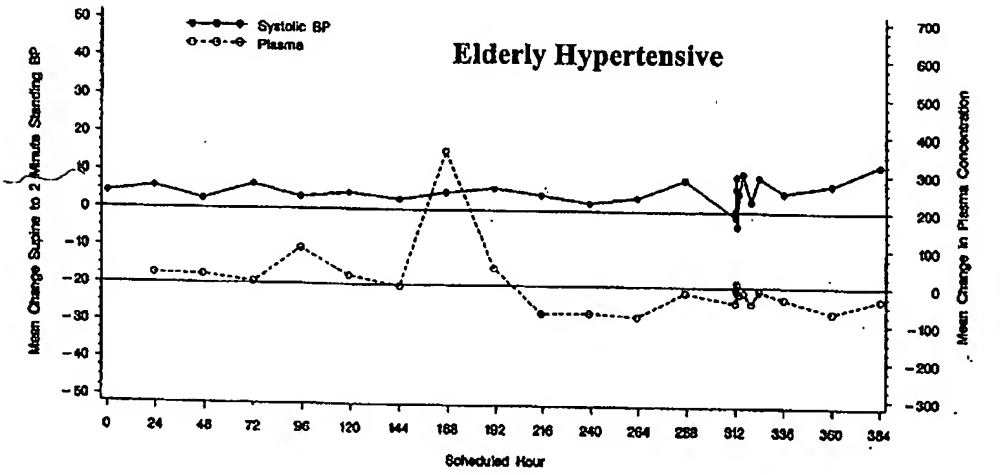
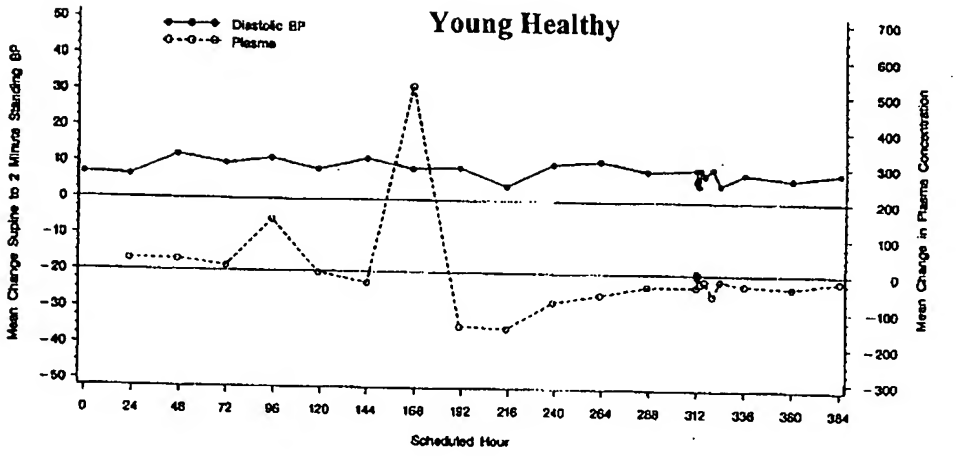
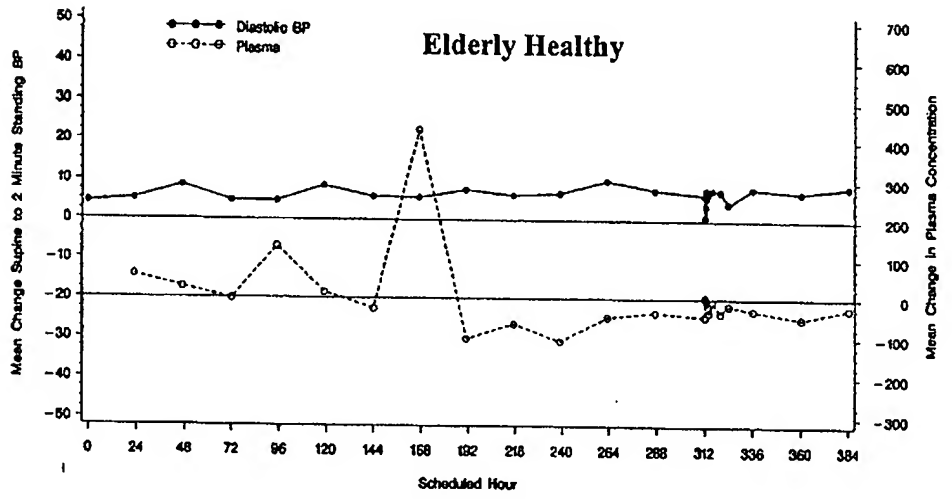

Elderly Hypertensive
Systolic BP
Plasma
Mean Change Supine to 2 Minute Standing BP
Mean Change in Plasma Concentration
Scheduled Hour

FIGURE 4


Young Healthy
Diastolic BP
Plasma
Mean Change Supine to 2 Minute Standing BP
Mean Change in Plasma Concentration
Scheduled Hour


Elderly Healthy
Diastolic BP
Plasma
Mean Change Supine to 2 Minute Standing BP
Mean Change in Plasma Concentration
Scheduled Hour

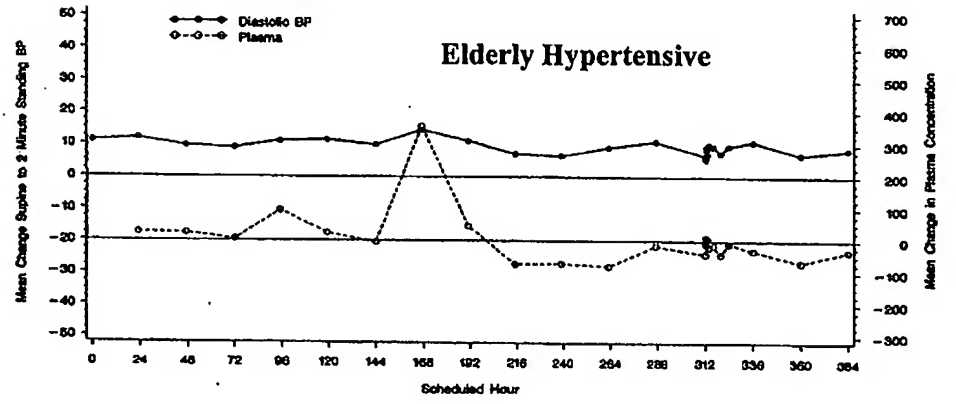

Elderly Hypertensive
Diastolic BP
Plasma
Mean Change Supine to 2 Minute Standing BP
Mean Change in Plasma Concentration
Scheduled Hour

FIGURE 5

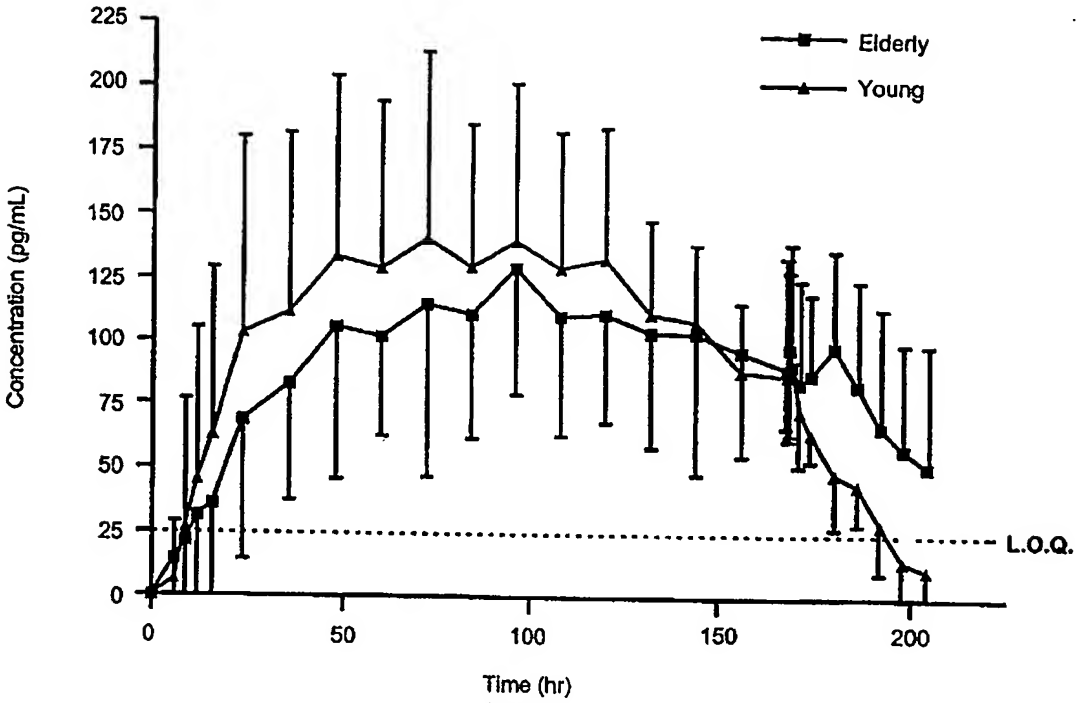

Elderly
Young
Concentration (pg/mL)
225
200
175
150
125
100
75
50
25
0
L.O.Q.
0
50
100
150
200
Time (hr)

FIGURE 6

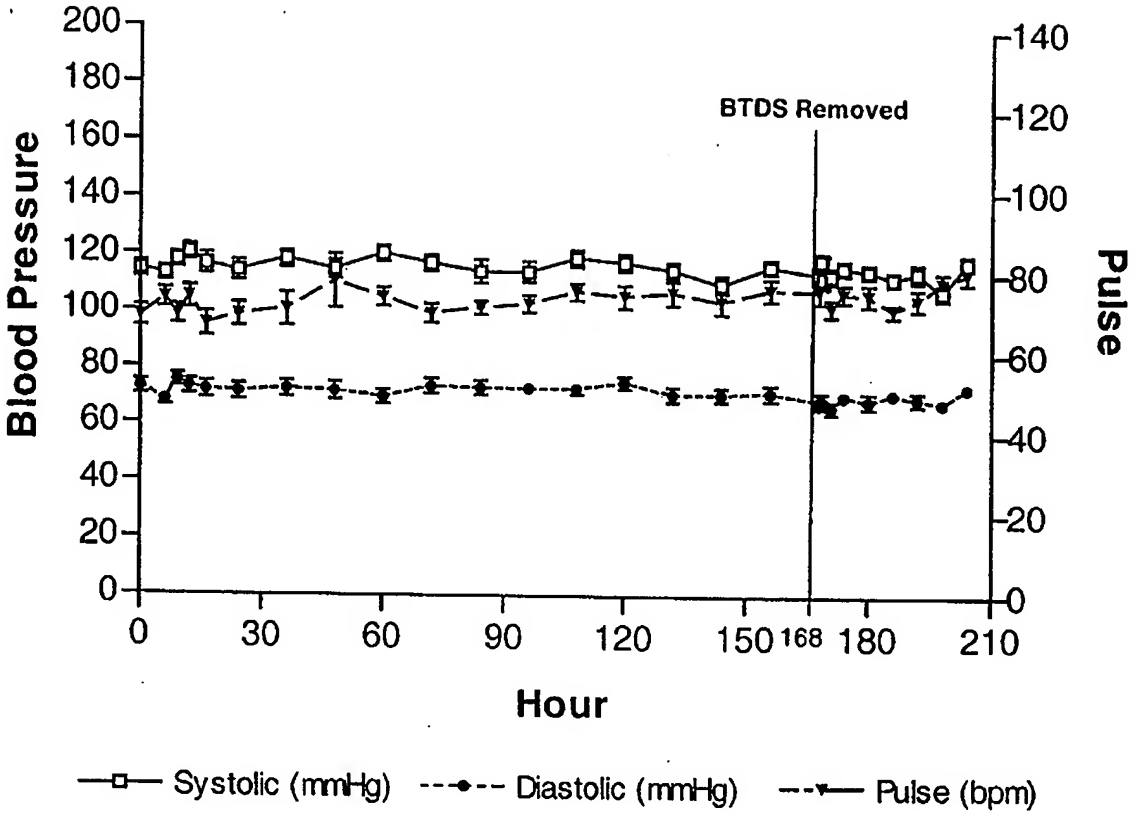

Blood Pressure
200
180
160
140
120
100
80
60
40
20
0
Pulse
140
120
100
80
60
40
20
0
BTDS Removed
0
30
60
90
120
150
168
180
210
Hour
Systolic (mmHg)
Diastolic (mmHg)
Pulse (bpm)

FIGURE 7

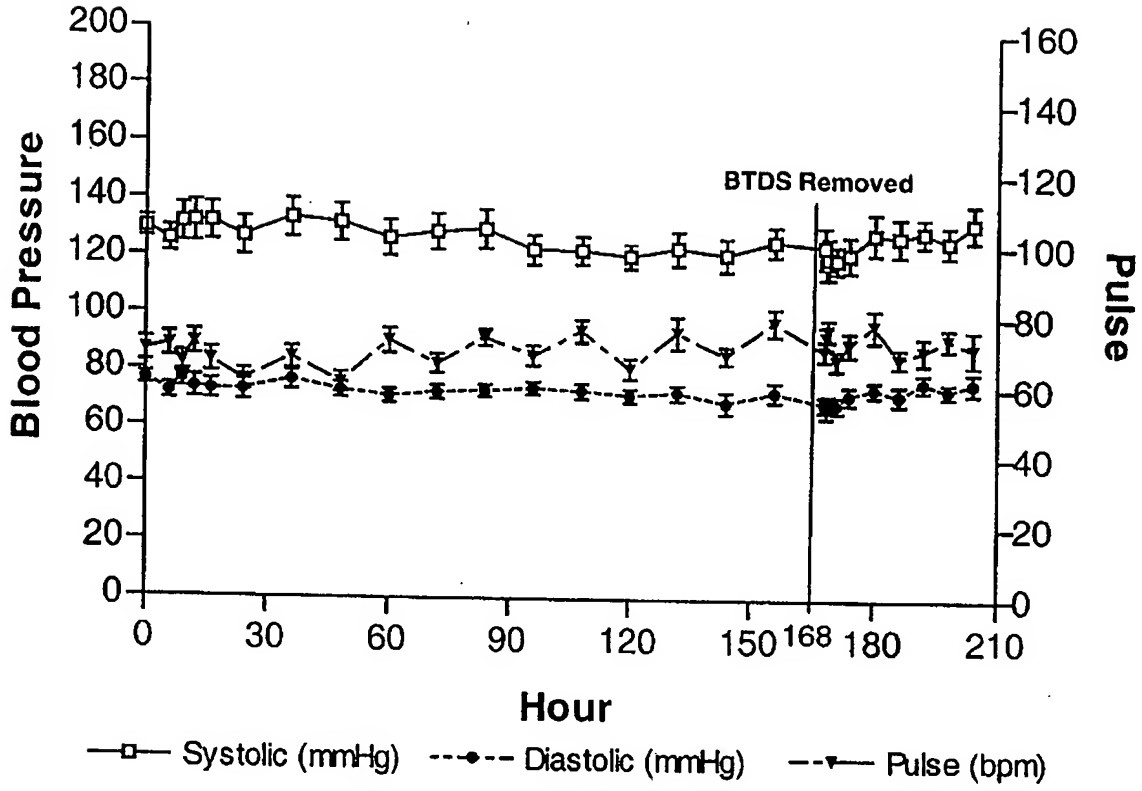
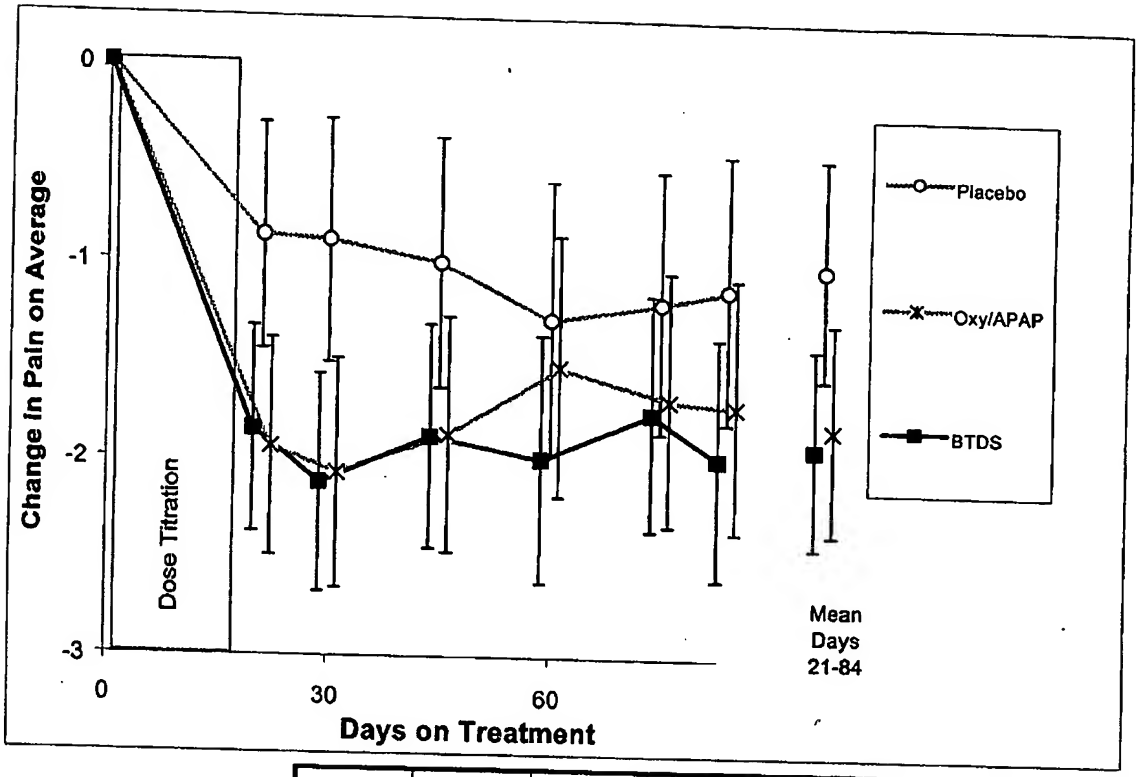

Blood Pressure
Pulse
BTDS Removed
Hour
Systolic (mmHg)
Diastolic (mmHg)
Pulse (bpm)

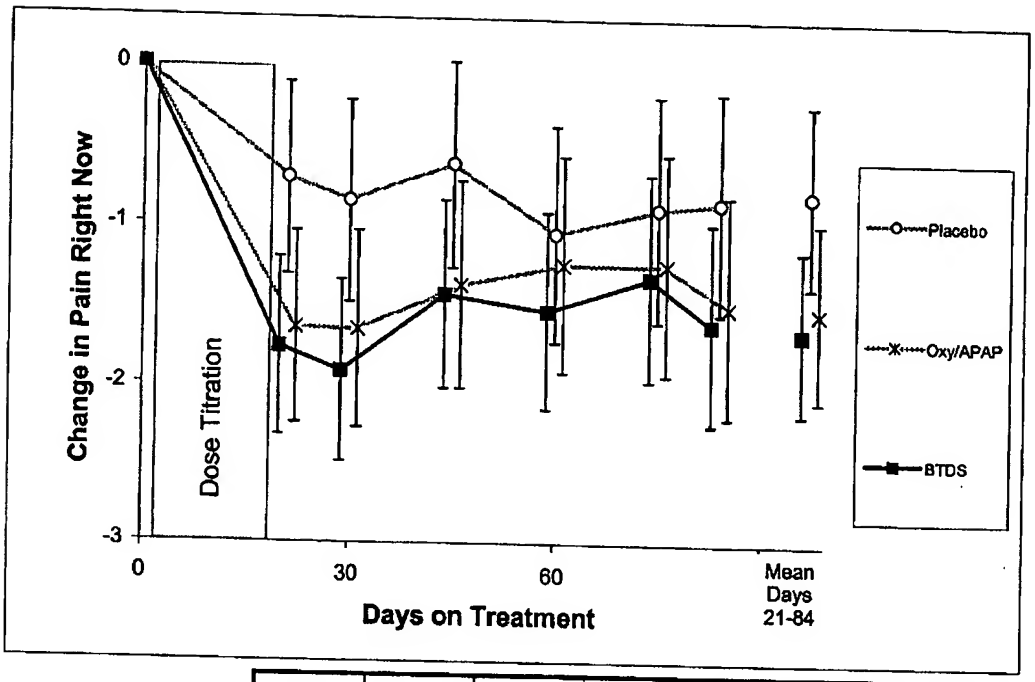
FIGURE 8



		Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	RM 21-84
Placebo N=45	LS Mean ± SEM	-0.87 ± 0.38	-0.89 ± 0.41	-1.00 ± 0.42	-1.28 ± 0.46	-1.19 ± 0.44	-1.12 ± 0.45	-1.01 ± 0.37
	N with data	34	23	22	18	18	18	45
Oxy/APAP N= 42	LS Mean ± SEM	**-1.94 ± 0.37**	**-2.07 ± 0.39**	-1.87 ± 0.40	-1.52 ± 0.44	-1.68 ± 0.43	-1.71 ± 0.43	-1.82 ± 0.36
	N with data	**31**	**32**	29	29	28	27	42
	Pairwise vs. Placebo	***P*=0.016**	***P*=0.013**	ns	ns	ns	ns	ns
BTDS N= 46	LS Mean ± SEM	**-1.85 ± 0.35**	**-2.12 ± 0.37**	-1.88 ± 0.38	-1.99 ± 0.42	-1.75 ± 0.40	-1.98 ± 0.41	**-1.92 ± 0.34**
	N with data	**33**	**29**	25	23	21	22	**46**
	Pairwise vs. Placebo	***P*=0.025**	***P*=0.0093**	ns	ns	ns	ns	***P*=0.035**

Least squares (LS) means - corrected by SAS Proc Mixed for baseline pain, center and opioid experience
Bar indicates time of dose titration: all BTDS patients started with BTDS 5 and titrated dose on Day 7 and/or Day 14
N = Number of patients with data at that visit; N for LOCF = N for the treatment group and was consistent over time
Bars at each data point indicate ± 1.5 SEM
RM 21-84 values calculated via repeated measures analysis of all available data from Days 21-84 using SAS Proc Mixed
Pairwise vs. Placebo - results of comparison with placebo using SAS Proc Mixed
ns = difference not statistically significant (P> 0.05)
Bolding indicates statistically significant reesults

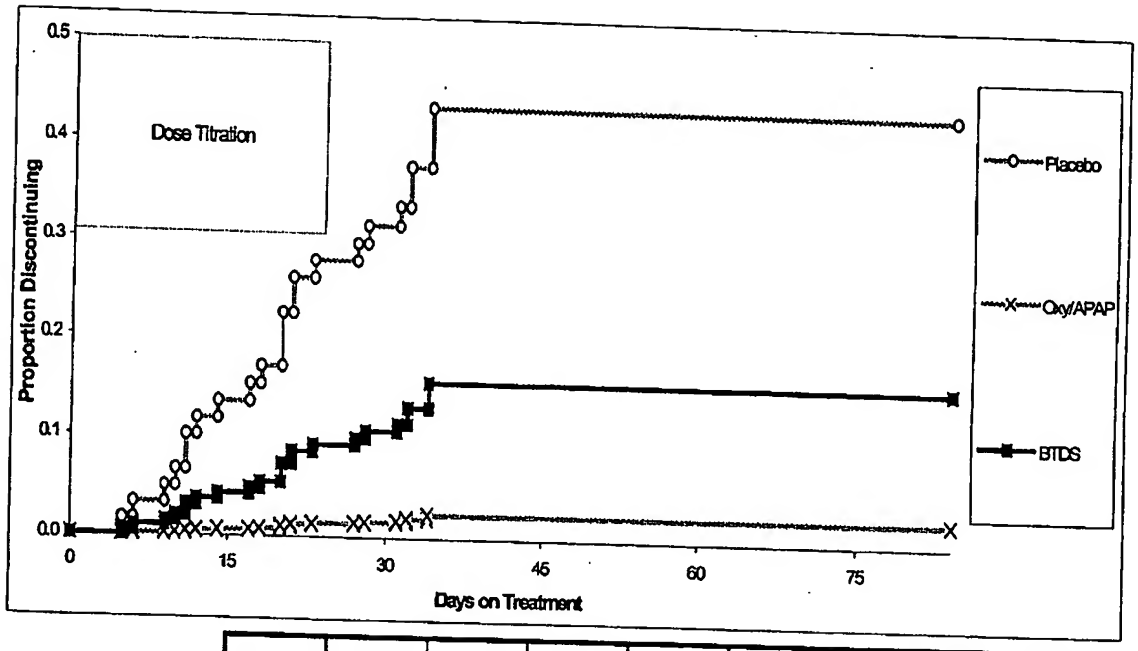
FIGURE 9



		Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	RM 21-84
Placebo	LS Mean ± SEM	-0.71 ± .040	-0.85 ± 0.42	-0.62 ± 0.43	-1.05 ± 0.45	-0.89 ± 0.47	-0.85 ± 0.46	-0.80 ± 0.38
N=45	N with data	34	23	21	18	18	18	45
Oxy/APAP	LS Mean ± SEM	**-1.64 ± 0.40**	-1.65 ± 0.41	-1.37 ± 0.43	-1.24 ± 0.45	-1.24 ± 0.46	-1.50 ± 0.46	**-1.53 ± 0.37**
N= 42	N with data	**31**	32	29	29	28	27	42
	Pairwise vs. Placebo	***P*=0.049**	ns	ns	ns	ns	ns	ns
BTDS	LS Mean ± SEM	**-1.76 ± 0.37**	**-1.91 ± 0.38**	-1.43 ± 0.39	-1.53 ± 0.41	-1.32 ± 0.43	-1.61 ± 0.42	**-1.66 ± 0.34**
N= 46	N with data	**33**	**29**	25	23	21	22	46
	Pairwise vs. Placebo	***P*=0.022**	***P*=0.028**	ns	ns	ns	ns	***P*=0.045**

Least squares (LS) means - corrected by SAS Proc Mixed for age category, baseline pain, center and opioid experience
Bar indicates time of dose titration: all BTDS patients started with BTDS 6 and titrated dose on Day 7 and/or Day 14
N = Number of patients with data at that visit; N for LOCF = N for the treatment group and was consistent over time
Bars at each data point indicate ± 1.5 SEM
RM 21-84 values calculated via repeated measures analysis of all available data from Days 21-84 using SAS Proc Mixed
Pairwise vs. Placebo - results of comparison with placebo using SAS Proc Mixed
ns = difference not statistically significant (P> 0.05)
Bolding indicates statistically significant results

FIGURE 10



	Day 0	Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	Days 0-84	Pairwise vs. Placebo
Placebo (N=45)									
Proportion discontinuing	0.000	0.260	0.315	0.435	0.435	0.435	0.435	-	
Number (at interval start)	45	29	26	22	19	19	18	-	
Drop out Lack of Efficacy	-	10	3	3	0	0	0	**16**	
Censored (total)	-	6	0	1	3	0	1	**11**	
Oxy/APAP (N=43)									
Proportion discontinuing	0.000	0.013	0.016	0.024	0.024	0.024	0.024	-	***P*=0.002**
Number (at interval start)	43	32	32	29	29	28	27	-	
Drop out Lack of Efficacy	-	0	0	1	0	0	0	**1**	
Censored (total)	-	11	0	2	0	1	1	**15**	
BTDS (N=46)									
Proportion discontinuing	0.000	0.086	0.107	0.157	0.157	0.157	0.157	-	***P*=0.011**
Number (at interval start)	46	32	29	25	23	22	22	-	
Drop out Lack of Efficacy	-	5	0	2	0	0	0	**7**	
Censored (total)	-	9	3	2	2	1	0	**17**	

Proportional hazards model using SAS proc PHREG with covariate correction for center and opioid experience
Bar indicates time of dose titration: all BTDS patients started with BTDS 5 and titrated dose on Day 7 and/or Day 14
ns = difference not statistically significant (P> 0.05)
Bolding indicates statistically significant results

FIGURE 11